Table 1 Acute effects of smoking; human studies

First author; Year of study	***Subjects (no); Smoking status***	***Design R (hrs); S (no); T(hrs)***	***Effect of smoking***
		Inflammation	
Abboud RT (1986)[1]	8 CS	R: 8 S: 8 in 2 hrs T: 0.5, 1, 2	Blood: NE ↑ 1 hr, leukocytes and neutrophils ↑ 1 and 2 hrs
Drost EM (1993)[2]	8 CS	R: 12 S: 2 T: direct	Blood: Leukocyte deformability ↓, NE ↑
Fauler J (1997)[3]	12 NS	R; ? S: 6 T: 12	Urine: LTE4 ↑
Gil E (1995)[4]	9 CS	R: ? S: 1 T: 15 min	EP* = in CS
Hockertz S (1994)[5]	5 CS, 5 NS	R: ? S: 24 in 8 hrs T: during	Blood: Granulocytes ↑, CD19 cells ↓, CD3 cells =, CD4/CD8 ratio =, IL-1 =, IL-6 =, PGE2 =, sCD14 =, ROI =
Kaplan JD (1992)[6]	7 CS, 7 NS	R: no S: 1 T: 30 min	Endothelial permeability† =
Kobayashi J (1988)[7]	23 CS	R: 12 S: 5 T: 0, 20 min	Blood: LTB4, LTD4 and LTE4 ↑, correlated positively to C3a en C5a
Janoff A (1983)[8]	11 CS, 11 NS	R: ? S: 2 T: 0.5-1	BALF: Elastase ↑, Neutrophils =, monocytes =, leukocytes =
MacNee W (1989)[9]	24 CS, 6 NS	R: not S: 3-6 T: during	Out wash of neutrophils‡ ↓
Patiar S (2002)[10]	12 CS	R: 12 S:4 T: 10 and 30 min	Blood: Granulocyte L-selectin expression ↑ 10 and 30 min
Skwarski KM (1993)[11]	8 CS, 8 NS	R: 12 S: 1 T: 5 min	RBC transit time across the mid and lower part of the lung ↓
Tardif J (1990)[12]	8 CS, 4 NS	R: 7 S: 4 T:1	BALF: AM release of LTB4 ↓
Walter S (1980)[13]	25 CS	R: 12 S: 2 T: 10 min	Blood: Basophils ↓
Walter S (1982)[14]	27 CS	R: 12 S: 1-2 T: 10 min	Blood: Basophilic degranulation ↑

Ward C (2000)[15]	5 CS, 5 NS	R: ? S: 1 T: 10 min	Endothelial permeability[§] ↑
Winkel P (1980)[16]	4 Female CS	R: 24 S: 12 in 3-4 hrs T: during	Blood: Lymphocytes ↓, Eosinophils ↓, Neutrophils ↑ after 2.5 hrs
		Oxidative stress	
Balint B (2001)[17]	15 CS, 15 NS	R: ? S: 2 T: 0.5 and 1.5	Breath condensate: Nitrate + nitrite ↑ 30 minutes, 90 minutes =, nitrite =, peroxynitrite = Exhaled air: eNO =
Chambers DC (1998)[18]	24 CS	R: ? S: 1 T: 1, 10 min	Exhaled air: eNO↑
Guatura SB (2000)[19]	12 CS, 10 NS	R: 10 S: 1 T: 30 min	Breath condensate: H_2O_2↑
Kharitonov SA (1995)[20]	17 CS	R: 8 S: 1 T: 5, 15 min	Exhaled air: eNO↓ 5 min, = 15 min
Morrison D (1999)[21]	14 CS, 7 NS	R: 12 S: 2 T: 1	BALF: Leukocytes O^{2-} ↑, TBARS =, TEAC ↑, GSH =, GSSG =, Neutrophils ↑ Blood: TEAC ↓, TBARS↑ EP[‡]: ↑
Morrow JD (1995)[22]	10 CS, 10 NS	R: 10 S: 3 T: 0.5	Blood: F2-isoprostane =
Montuschi P (2000)[23]	12 CS	R: 12 S: 2 T: 15 min, 5	Breath condensate: 8-isoprostanes ↑ 15 min, = 5 hrs
Rahman I (1996)[24]	12 CS, 14 NS	R: ? S: 1 T: 1	Blood: TEAC↓, TBARS ↑
Tsuchiya M (2002)[25]	20 CS	R: ? S: 1 T: 5 and 30 min, 1	Blood: Nitrate, nitrite, ascorbic acid, cysteine, methionine, uric acid 5 min ↓, 30 min =

Definition of abbreviations:
CS: cigarette smokers NS: non-smokers R: time refrained from cigarette smoking (hrs) S: number of cigarettes smoked T: time between smoke inhalation and measurements (hrs)

AMs: alveolar macrophages; eNO: exhaled nitric oxide; EP: epithelial permeability: PGE2; prostaglandin E2; ROI: reactive oxygen intermediates; TEAC: trolox equivalent anti-oxidant capacity; TBARS: thiobarbituric acid reactive substances; LTB4: leukotrien B4; GSH: gluthatione; GSSG: oxidised gluthatione; NE: neutrophil elastase

[*] ^{99m}Tc-DTPA-scan
[†] PET
[‡] ^{111}-In labelled neutrophils
[§] Radioactive Urea

Table 2 Acute effects of cigarette smoking; animal studies

First author; Year of study	*Animals (no)*	*Smoke exposure S (no); E (hrs); T (hrs)*	*Route of administration*	*Effect of smoke exposure*
			Inflammation	
Abrams WR (1988)[26]	Beagle dogs N=12	S: 1, 3 or 6 E: ? T: 1, 4, 15, 24	AM	BALF: 3 and 6 cig: PMNs ↑ 15 hrs, = 1, 4 and 24 hrs 6 cigarettes: EIC ↑ 1 hr 3 cig: Elastase/PMN ↓ 4, 15 hrs, = 24 hrs
Bosken CH (1991)[27]	New Zealand White rabbits N= 5 CS, 5 NS	S: 12 puffs E: 12 min T: 4, 7 12 min	IT	Histology: PMNs retention in lungs ↑, PMNs retention in lowest lung slices ↑ Blood: MPO ↑ 4 and 7 min, = 12 min EP* =
Boucher RC (1980)[28]	Guinea Pigs N=10-15	S: 5 - 100 puffs E: ? T: direct	IT	EP† ↑ after 40 puffs and 100 puffs EM: 100 puffs ↑ intercellular spaces and structural changes in tight junctions of tracheal segments
Burns AR (1989)[29]	Guinea Pigs; N= 25	S: 15 E: ? T: direct	M&N	Lung tissue: Focal disruptions in type I pneumocytes, epithelial desquamation, trans epithelial FITC-D penetration, FITC-D intracellular in type I pneumocytes EP*↑
Churg A (2002)[30]	C57BL/6 mice N= 4 CS, 4 NS	S:4 E: ? T: 24	N	Lavage: PMNs, AMs, desmosine and hydroxyproline ↑ 24 hrs No effect of smoke in MME knock-out mice, except AMs↑ Lung tissue: α-1-antitrypsin ↑ 24 hrs
Churg A (2002)[31]	C57BL/6 mice N= 5 CS, 5 NS	S: 4 E: ? T: 2, 6, 24	N	Lung tissue: TNF-α, MIP-2 and MCP-1 gene expression ↑ 2 hrs, = 6, 24 hrs Lavage: Desmosine, hydroxyproline, PMNs and AMs ↑ 24 hrs No smoke effect in TNF-α receptor knock-out mice
Churg A	C57BL/6 mice	S: 4 E: 1 T: 2, 6,	N	Gene expression 2 hrs: TNF-α ↑, MCP-1 ↑, MIP-2

(2003)[32]	N=3 CS, 3 NS	24		↑, 6 hrs: TNF-α =, MCP-1 =, MIP-2 ↑, protein: TNF-α ↑ 2, 6, 24 hrs, E-selectin ↑ 6 and 24 hrs MMP-12 knock-out mice no effect on gene upregulation, but inhibits effect on TNF-α and E-selectin
Daffonchio L (1990)[33]	Dunkin-Hartley guinea pigs N= ?	S: ? E: 10 min T: 5, 50 min	IT	BALF: 5 min: total cells ↑, neutrophils =, eosinophils ↑, macrophages ↑ 50 min: total cells ↑, neutrophils =, eosinophils =, macrophages ↑
Dhami R (2000)[34]	C57-BL/6 mice N= 5 CS, 5 NS	S:2 E: ? T: 6, 24	N	BALF: PMNs ↑ 24 hrs, AMs = 24 hrs, desmosine ↑ 6, 24 hrs, hydroxyproline ↑ 6, 24 hrs, serine and metalloelastase activity↑ Anti-PMN and α-1 AT: inhibit smoke effect on PMNs, desmosine, hydroxyproline and serine elastase activity
Holt PG (1973)[35]	C57 black inbred mice N= 10	S: 30 E: 8 min T: direct	SM	Lavage: Viability AMs ↓
Hulbert WC (1981)[36]	Camm Hartley Guinea Pigs N= 30	S: 100 puffs E: ? T: 30 min, 1, 6, 12, 24	IT	EP†: ↑ 30 min, = 24 hrs Histology: Exudate↑ 0.5-1 hr, = 6, 12, 24 hrs, Cells expressed per mm epithelial cells: PMNs↑ 6 hrs, basal membrane ↓ 0.5-6 hrs, ↑ 24 hrs, goblet cells ↓ 0.5-12 hrs, plasma cells ↓, eosinophils ↓ 6, 12 and 24 hrs, mast cells ↑ 6 hrs, = 12 hrs
Ischizaki T (1996)[37]	Sprague-Dawley rats N=103, groups of 6-15 rats	S: 5 E: 20 min T: 2, 6, 24	SC	Plasma EIC ↓ 2 hrs, =6 and 24 hrs Plasma ferroxidase activity ↓ 2 hrs, = 6 and 24 hrs, plasma lipid peroxide ↑ 2 and 6 hrs, =24 hrs Lung tissue: lipid peroxide = 2 hrs, ↑ 6 hrs, = 24 hrs, GSH ↓ direct, ↑ 2 and 6 hrs, ↓ 24 hrs, GSH/GSSG ratio ↓ 2, 6 and 24 hrs BALF: total cell count and neutrophils↑ 24, AM and lymphocytes = 24 hrs
Janoff A	Sprague-	S: 3 or 6 puffs E:	SC	BALF: EIC per α-1 AT↓, after adding reducing

(1979)[38]	Dawley rats N= 21 CS, 16 NS	? T: direct		agent recovery of 75% of EIC
Kew RR (1985)[39]	Sprague-Dawley rats N= 4 CS, 4 NS	S: 12 puffs E: 4 min T: 1	SC	BALF: 1 hr: C3 ↑, PMNs ↑, monocytes↑, leukocyte chemotactic activity↑, prevented by depletion of complement
Kilburn KH (1975)[40]	Syrian hamsters N= 3	S: ? E: 4 T: 2, 8, 20	N	Histology: Ratio PMN/ 100 epithelial cells time dependent ↑ 6-24 hrs
Li XY (1996)[41]	Rats N=16	S: ? E: 0,2 ml CSC T: 1, 6, 24	IT	EP‡: ↑ 6 hrs, = 24 hrs BALF: AMs and PMNs ↑ 1, 6 and 24 hrs, GSH ↓ 1, 6 hrs, GSSG ↑ 1 hr, = 24 hrs Lung homogenate: GSH ↓ 1 hr, = 6 hrs, GSSG: ↑ 1 hr, ↓ 6 hrs, = 24 hrs
Mordelet-Dambrice M (1991)[42]	Wistar rats N= 28 CS, 28 NS	S: 32 puffs E: 8-9 min T:15 min	N	EP§: ↑ 15 min BALF: AMs ↑, PMNs =
Nishikawa M (1990)[43]	Hartley Guinea Pigs N= 46 CS, 18 NS	S: 5, 10 or 20 puffs E: ? T: direct, 5, 24	N&M	EP ‖: = Histology: Neutrophils and eosinophils in the trachea =
Ortega E (1992)[44]	Swiss mice IFFA CREDO N= ?	S: 1 E: 15 min T: direct, 1, 12, 24	SC	Histology: AMs ↑ direct and 1 hr, phagocytic index ↓ direct and 1 hr, = 12 hrs, % activated AMs ↑ direct, phagocytic efficiency ↓ direct and 1 hr
Ortega E (1993)[45]	Mice N= ?	S: 1 E: 15 min T: 1	SC	Adherence AMs =, chemotaxis AMs =, phagocytosis of Candida Albicans ↓
Pessina GP (1993)[46]	Out bred Wistar rats N= 12	S: 3 E: 1 T: 8, 24	SC	BALF: AMs ↑ 8 hrs, PMNs ↑ 24 hrs, TNF-α release from AMs ↑ 8 hrs, IFN release from AMs =
Pessina GP (1996)[47]	Wistar rats N= 6 CS, ? NS	S:3 E: ? T: direct	SC	BALF: Degradation of IL-6 ↑
Reznik-Schuller HM	Syrian Hamster	S: 20 puffs E: ? T: 1	SM	EM: Haemorrhages, swollen cytoplasm and protrusions in the lumen of type I pneumocytes and

(1980)[48]	N= 40 CS, 40 NS			endothelial cells. Occasionally the cell membrane was ruptured.
Simani AS (1974)[49]	Guinea Pigs N= 67	S:1 or 10 E: 24 hrs T: direct	M&N	EP† = after 1 and 10 cigarettes EM: Tight junctions ↑ after 10 cigarettes
Vitalis TZ (1998)[50]	Guinea Pigs N= 6 CS, 6 NS	S: 5 E: 40 min T: direct	N	Lung parenchyma: AMs↑ Airway wall: PMNs ↑
Walker DC (1988)[51]	Hartley Guinea Pigs N= 30 CS, 5 NS	S:15- 100 puffs E: ? T: direct	M&N	No increased HRP in epithelial tight junctions of tracheal segments
Witten ML (1985)[52]	New-Zealand white rabbits N =12 CS, 6 NS	S: 5-30 breaths E: ? T: during	IT	EP§:↑ from 20 breaths EM: Focal alveolar edema and haemorrhage, no alveolar-capillary membrane damage
Witten ML (1988)[53]	Rabbits N= 6 CS, 6 NS	S: 5-30 breaths E: ? T: direct	IT	EP§:↑ during smoking, Ibuprofen ↑ EP EM: Focal alveolar edema BALF: TxB2 ↑, 6keto PGF1α ↑, lymphocytes ↓, LTB4 ↓ Blood: LTB4 =, TxB2 =, 6keto PGF1α ↑
Wright J (1990)[54]	Guinea pigs N= 8 CS, 8 NS	S: ? E: 15 min T: 15 min, 1.5	IT	BALF: 1.5 hrs: leukocytes =, PMNs ↑ Blood: 15 min: leukocytes and PMNs ↑
Wright JL (2002)[55]	C57BL/6 mice N= 6	S: 4 E: ? T: 2	N	Mice: Lung homogenate: mRNA MIP-2, MCP-1, TNF-α ↑ 2 hrs Plasma: TNF-α ↑ 2 hrs
	Guinea Pigs N= 5	S: 5 E: 3-4 T: 24		Guinea Pigs: BALF: PMNs, desmosine, hydroxyproline ↑ 24 hrs Neutrophil elastase inhibitor: prevented smoke effects, except on TNF-α mRNA
Yamaya M (1989)[56]	Mongrel dogs N= 40	S: 1, 3, 5 or 9 E: ? T: direct, 7, 14	IT	BALF: Cytoplasmic motility AMs↑ direct, = 7 min after 1, 3 or 5 cigarettes

		min		
		Oxidative stress		
Aoshiba K (2003)[57]	C57-BL/6 mice N=6	S: 10 E: 1 T: 1, 3, 16, 24	SC	Lung tissue: 8-OHdG and 4-HNE ↑ 1 hr in bronchial epithelial cells and type II alveolar cells, cellularity ↑ 1-16 hrs, BALF: 8-OHdG levels ↑ 1 hr, = 24 hrs
Bilimoria MH (1992)[58]	Sprague-Dawley rats N=8 Hartley GP N=?	S: 40, 120, 240 puffs E: ? T: direct and 3	N	Lung homogenate: GSH ↓ direct, = 3 hrs, Ascorbic acid = direct
Cavarra E (2001)[59]	C57-BL/6J mice N=35 CS, 70 NS	S: 5 E: 20 min T: direct, 20, 60 min	SC	BALF: TEAC ↓ direct, = 20 min BALF, direct: GSSG ↑, ascorbic acid ↓, protein thiols ↓, total gluthatione =, vitamin E =, 8-epi-PGF2α ↑, all prevented by NAC Plasma: 8-epi-PGF2α ↑ direct, 20 and 60 min Total cell count, AMs, PMNs and lymphocytes = Inactivation of human SLPI
Cotgreave IA (1987)[60]	Sprague-Dawley rats N= ?	S:10 E: 1 T: direct	N	BALF: Intracellular GSH ↓, free GSH in lavage fluid ↓ Blood: GSH =, Cysteine ↑ Lung tissue: Cysteine =, Intracellular GSH
Uotila P (1982)[61]	Syrian hamsters N= ?	Experiment 1¶: S: 5 E:1 T: 20 Experiment 2**: S:12 E: 2 T: during	SC	Experiment 1: Blood: MUG ↑ 20 hrs Experiment 2: Blood: MUG ↓ during smoking
Wright JL (1999)[62]	Rats N= ?	S: 7 E:2 T: 24	N	Lung homogenate: 24 hrs: cNOS mRNA and protein =, iNOS mRNA ↑, protein =, eNOS mRNA ↑, protein =

Definition of abbreviations:
S: number of cigarettes exposed (no) E: exposure time (hrs) T: time between smoke exposure and measurement (hrs)
AM: anesthesia mask; IT: intra tracheal inhalation; N: nose-only inhalation; N&M: nose and mouth inhalation; SC: smoking chamber; SM: smoking machine

α-1 AT: α-1 antitrypsin; BALF: broncho-alveolar lavage fluid; CS: cigarette smoking animals; CSC: cigarette smoke condensate; EIC: elastase inhibitory capacity; EM: electron Microscopy; EP: Epithelial permeability; FITC-D: fluorescein isothiocyanate-dextran GSH: Gluthatione; HRP: Horseradish Peroxidase; ^{125}I-BSA= 125 Iodine labelled Bovine Serum Albumin; MME: macrophage metalloelastase; NOS: nitric oxide synthase; 6keto PGF1α: stable metabolite of prostacycline, prostaglandin I_2; MCP-1: macrophage chemoattractant protein-1; MIP-2: macrophage inhibitory protein-2; MPO: myeloperoxidase; MUG: 4- methylumbelliferone glucuronide; NS: non-smoking animals; PMNs: polymorphonuclear cells; SLPI: secretory leukoprotease inhibitor; TxB2: stable metabolite of tromboxane A_2

[*] Measured by FITC-D inhalation
[†] Measured by HRP
[‡] Measured by ^{125}I-BSA
[§] Measured by ^{99m}TcDTPA
[ll] Measured by wash out of Evans Blue
[¶] Lungs were isolated, ventilated with cigarette smoke and thereafter perfused with MUG.
[**] Isolated lungs were simultaneously ventilated with cigarette smoke and perfused with MUG.

Table 3 Acute effects of cigarette smoke exposure; in vitro studies

First author; Year of study	***Cell types***	***Smoke exposure S (cig/ml); E (hrs); T (hrs)***	***Effect of smoke exposure***
		Inflammation	
Aoshiba K (2001)[63]	Murine, rat and human AMs	CSE: S: 0.1 E: 4-24 T: 4-24	24 hrs: 93% of AMs in apoptosis*, inhibition by anti-oxidants
Brown GM (1991)[64]	Human PMNs	CSE: S: 1 cig E: 4 min T: 4 min	NE = 4 minutes PMNs: Extensive blebbing of cell membranes
Bridges RB (1977)[65]	Human PMNs	CSE: S: ? E: ? T: ?	Chemotaxis of PMNs ↓ concentration dependent
Cantral DE (1995)[66]	BBEC	CSE: S: 0.01 E: 2, 6, 24 T: 2, 6, 24	2 and 6 hrs exposure: attachment† of BBEC ↓, cell migration 2, 6 and 24 hrs = 24 hrs exposure: attachment† of BBEC ↑
Carnevali S (1998)[67]	HFL-1	CSE: 0.0016-0.0024 E: 24 T: 24	Fibroblast-mediated collagen gel contraction ↓ PGE2 release =, α2β1 integrin expression =, fibronectin release ↓
Carnevali S (2003)[68]	HFL-1	CSE: S: 0.002-0.004 E: 3 T: 3	Intracellular H_2DCFDA ↑ Apoptosis‡ ↑, prevented by NAC Intracellular GSH ↓, inhibited by NAC DNA fragmentation ↑, inhibited by NAC
Churg A (2003)[32]	Mice AMs	CSE: S: 0.3 E: 18 T: 18	TNF-α release ↑
Drost EM (1992)[69]	Human PMNs	CS: S: 1, 3, 5 puffs E: 4 min T: 4 min	PMN filtration pressure ↑ after 1, 3, or 5 puffs, no effect of anti-CD18, inhibited by anti-oxidants and actin filaments cytoskeletal inhibitors Release H_2O_2 ↓
Dubar V (1993)[70]	Guinea pig and human AMs	CS: S: 2 E: ? T: ?	Activity of IL-6 and TNF-α ↓
Falk HL (1959)[71]	Ciliated epithelium from fogs, rat and rabbit trachea	CS: S: 50 ml E: 2 sec T: 1, 16, 46 min CSE: S:0.5 E: 2-30 sec T: 1, 16, 46 min	Mucus flow along epithelium ↓ 1-46 minutes
Floreani AA	Primary	CSE:	Adhesion THP-1 monocytes to HBEC ↑, inhibited by

(2003)[72]	HBECs BEAS-2B	S: 0.020 E: 1 T: 1	anti-TNF-α ICAM-1 expression HBEC ↑ Adhesion AMs, THP-1, peripheral blood monocytes to BEAS-2B↑
Green GM (1967)[73]	Rabbit AMs monolayer	CSE: S: 1-4 ml CS/ml E: ? T: 2	Phagocytosis staphylococcus albus ↓ dose dependent
Higashimoto Y (1991)[74]	Mice AMs	CSE: S: 0.04-0.001 E: 1 T: 1	TNF-α↓
Hellerman GR (2002)[75]	HBEC	CSE: S: ? E: 30 min T: 30 min	mRNA of IL-1β, IL-8, IL-6, GM-CSF, ICAM-1, RANTES ↑
Holt PG (1972)[76]	Rabbit AMs, murine PMs, secondary cultured murine embryonic fibroblasts	CS: S: 0.5- 2 puffs E: 4 sec T: 30 min-24 CSE: S: 35 ml smoke E: 70 min T: 70 min	CS: AMs and PMs: 30 min viability ↓ and ^{3}H-protein synthesis ↓, 24 hrs = Fibroblasts: 30 min viability =, ^{3}H-protein synthesis 30 min and 24 hrs ↓ CSE: macrophages and fibroblasts: ^{3}H-protein synthesis decreased dose dependent
Holt PG (1973)[35]	Primary cultured mice AMs, PMs, fibroblasts	CS: S: ? E: 60 sec T: 30 min, 24	30 minutes: viability AMs and PMs ↓, fibroblasts = 24 hrs: viability PMs and fibroblasts ↓ RNA synthesis of survivors ↑
Hoshino Y (2001)[77]	A549 cell line	CSE: S: 0.008 - 0.01 E: 3, 12, 24 T: 3, 12, 24	Cell viability ↓ time and dose dependent 3 hrs 0.8% CSE: ↑ oxidative activity in cells, inhibited by NAC
Ishii T (2001)[78]	HFL1	CSE: S: 1 E: 4, 8, 12, 16, 20, 24 T: 4, 8, 12, 16, 20, 24	10-25% CSE → Apoptosis‡ 20, 24 hrs 50-100% CSE → Necrosis§ 4-48 hrs GSTP1 sense vector ↓ necrosis 20, 24 hrs, apoptosis = GSTP1 anti-sense vector ↑ necrosis 4-48 hrs, apoptosis =
Kalra VKE (1994)[79]	Human monocytes, HUVEC	CSE: S: 10-60 μg/ml E: 5-90 min T: 5-90 min, 2-24 hrs	CD11b expression monocytes ↑ time dependent, optimum after 25 min exposure Adhesion monocytes to HUVEC ↑, 30 min exposure HUVEC: ICAM-1 and ELAM-1 ↑ 8, 24 hrs (60 min exposure)
Kim HJ (2002)[80]	HFL-1	CSE: S: 0.0004 E: 24 T: 24	Collagen gel contraction ↓ Fibronectin release ↓, prevented by NAC Intracellular GSH ↓, prevented and repleted by NAC EIIIA and B fibronectin mRNA ↓
Koyama S	Bronchial	CSE	MCA ↑ dose dependent

(1991)[81]	epithelial cell monolayers	S: 0.004 E: 2, 6, 24 T: 2, 6, 24	MCA ↑ after 2 hrs, time dependent Arachidonic metabolites inhibitors: ↓ MCA
Lannan S (1992)[82]	Human PMNs	CSE: 4 puffs E: 4 min T: 4 min	Diameter and circumference of neutrophils ↑ Surface membrane blebbing ↑
Lannan S (1994)[83]	A549 cell line	CS: S: 1 cig E: 5 min T: 5 min CSE: S: 1 E: during smoke exposure T: during smoke exposure	CS: Attachment[II] ↓ 45 min- 24 hrs, prevented by GSH CSE: Detachment[II] ↑, prevented by GSH, augmented by depleting GSH CSE: Proliferation ↓, prevented by GSH
Marwick JA (2002)[84]	A549 cell line	CSE: S: 10% E: 4, 24 T: 4, 20, 24	P21wafl/cip1 mRNA = 4 hrs, ↑ 24 hrs HDAC mRNA = 4, 24 hrs HDAC-2 protein 20 hrs ↓
Masubuchi T (1998)[85]	A549 cell-line	CSE S: 0.002 E: 12, 24 T: 12, 24	NCA = 12, 24 hrs
Mio TD (1997)[86]	HBEC	CSE: S: 0.004 E: 12-24 T: 12-24	IL-8 release ↑ concentration dependent IL-8 release ↑ time dependent, 12- 48 hrs. mRNA IL-8 ↑ 12 hrs
Nakamura Y (1995)[87]	HFL1	CSE: S: 0.002 E: 1-24 T: 1-24	Proliferation fibroblast: = 1 hr, ↓ 24 hrs
Niki E (1993)[88]	Rabbit erythrocytes	CSE: S: ? E: ? T: ?	Haemolysis rabbit erythrocytes, anti-oxidants no protection.
Ouyang Y (2002)[89]	HUVEC	CSE S: ? E: 24 T: 24	sICAM =
Richter A (2002)[90]	NCI-H292	CSE: S: 0.002 E: 6, 24 T: 6, 24	6 hrs: IL-8 mRNA ↑, TGF-α mRNA =, AR mRNA ↑, HB-EGF mRNA↑ 24 hrs: HB-EGF mRNA ↑
Robbins RA (1992)[91]	BBEC, human PMNs, mononuclear cells	CSE: S: 0.004 E: 24 T: 24	Adherence of PMNs to BBEC ↑
Rusznak C (2000)[92]	HBEC from HS, CS and COPD patients	CS: S: 4 E: 20 min T: 20 min	EP ↑ in all groups, COPD> HS> CS Il-1β and sICAM ↑ 24 hrs
Rusznak C (2001)[93]	HBEC	CS: S: ? E: 20 min, 1, 3, 6; T: 20 min, 1, 3, 6	20 min: IL-8 ↑, sICAM↑, IL-1β ↑ 1 hr: IL-8 ↓, IL-1β ↑ 3 and 6 hrs: IL-1 β ↓, IL-8 ↓, sICAM ↓

Ryder MI (1998)[94]	Human blood neutrophils	CS: S: ? E: 1-5 min T: 1-5 min	CD18 expression ↑ after 5 min L-selectin expression ↓ 1-5 min
Ryder MI (2002)[95]	PBMCs from 8 CS and 8 NS	CS: S:? E: 1, 2, 5 min T: 1, 2, 5 min	IL-1β ↑ 5 min in NS group TNF-α = TGF-β =
Sato E (1999)[96]	HFL1	CSE: S: 0.004 E: 6, 12, 24 T: 6, 24	MCA and NCA 24 hrs ↑, both inhibited by lipoxygenase inhibitors, anti-GM-CSF and anti-LTB4; NCA inhibited by anti-IL-8, MCA inhibited by, anti-MCP-1 mRNA IL-8, GM-CSF and MCP-1 ↑ 6 hrs
Selby C (1992)[97]	Human PMNs	CS: S: 1-4 cig E: 4 min T: 4 min	Basal adherence[¶] ↓ CD18 expression =, no effect of GSH Neutrophil chemokinesis ↓ Chemotaxis =
Shen Y (1996)[98]	HUVEC	CSE: S: 25 μg/ml E: 30 min-8 T: 30 min-8	ICAM-1, ELAM-1, VCAM-1 ↑
Shoij S (1995)[99]	Bovine epithelial cells	CSE: S: 0.04 E:3, 6, 12, 24 T: 3, 6, 12, 24	Dose and time dependent ↑ NCA from 3 hrs, inhibition by lipoxygenase inhibitors
Takeyama K (2001)[100]	NCI-H292	CSE: S: 0,5 puff/ml E: 15 T: 6, 12, 24	EGFR mRNA and MUC5AC mRNA ↑ 6-12 hrs MUC5AC protein ↑ 24 hrs dose dependent, inhibition by anti-oxidants
Tardiff J (1990)[12]	Human AMs	CSE: S: 0.04 E: 1 T: 1	Unstimulated AMs: LTB4 = PMA stimulated AMs: LTB4 ↓
Thomas WR (1977)[101]	Murine PMs	CS: S: 0.5-2 puffs E:? T: 30 min, 2, 3, 5, 24	Dose dependent ↓ of viability and phagocytosis of Pseudomonas aeruginosa 2 puffs: phagocytic activity ↓ 30 minutes and 24 hrs 1 puff: phagocytic activity ↓ at 2 hrs,↑ 5 hrs
Vayssier M (1998)[102]	U-937 cell line	CSE: S: 0.003-0.1 E: 4-16 T: direct	Low CSE: apoptosis[‡] 16 hrs High CSE: necrosis 16 hrs HSP70 expression ↑ dose dependent BCL-2 expression ↑ dose dependent
Vayssier-Taussat M (2001)[103]	Human PBMCs TrHBMECs	CSE: S: 0.3-2.4 E: 4, 16 T: 4, 16	Low CSE: at 4h: HSP70 and HO-1 expression ↑, at 16 hrs apoptosis[‡], inhibited by NAC High CSE: HO-1 expression ↓, at 16 h: necrosis, inhibited by NAC
Voisin C	Guinea pig	CS:	Viability AMs ↓ dose dependent, inhibited by NAC

(1985)[104]	AMs	S: 1-5 cig E: ? T: direct-3	Bactericidal activity of AMs ↓, inhibited by NAC
Wang HY (2000)[105]	ECV304	CSE: S: ? E: 2, 4, 8 T: 2, 4, 8	Time and dose dependent ↑ IL-8 secretion 4-8 hrs
Witherden IR (1997)[106]	Primary human alveolar type II cells	CSE: S: 0.01- 0.05 E: 24 T: 24	0.01 Cig/ml: IL-8 release ↑ 0.05 Cig/ml: cytotoxity
Wirtz HR (1996)[107]	Rat alveolar type II cells	CSE: S: 0.04 E: 0-1 T: 0-5	Surfactant secretion dose and time dependent ↓ from 20 min, no effect anti-oxidants
Yeager H (1968)[108]	Rabbit AMs	CSE: S: ? E: 20-120 min T: 20-120 min	Protein synthesis ↓ dose and time dependent
York GK (1973)[109]	Sheep AMs	CSE: S: 0.1 E: ? T: ?	Dose dependent ↓ of O_2 consumption Cell viability ↓
Zappacosta B (2001)[110]	Human PMNs	CSE S: ? E: 40 min T: during exposure	Phagocytic capacity ↓
Zhang X (2000)[111]	Human PBMCs	CSE: S: 1 E: 3 T: 3	TNF-α, IL-1β, IL-2 and IFN-γ ↓ dose dependent
		Oxidative stress	
Bridgeman M (1991)[112]	Erythrocytes, neutrophils, A549 cell line	CS: S: 1, 3, 5 puffs E: ? T: ?	Intracellular GSH ↓, no effect reducing agents
Hobson J (1991)[113]	Rat tracheal explants	CS: S: 1, 3, 6 puffs E: 10 min T: 40 min	H_2O_2 and O^{2-} ↑ along epithelial cell-membranes, prevented by SOD 3 and 6 puffs: cell separation, focal membrane blebbing, loss of cilia, cell disintegration.
Hoyt JC (2003)[114]	LA-4 A549 cell line HBEC	CSE: S: 0.0004-0.00008 E: 4, 24 T: 4, 24	Cells were stimulated for increased iNOS expression: CSE: nitrate ↓ 4 and 24 hrs in all cell types CSE: iNOS positive LA-4 cells ↓ 24 hrs CSE: iNOS mRNA ↓, eNOS and nNOS mRNA = in LA-4 cells 24 hrs, eNOS in A549 cells = 24 hrs
Kayyali US (2003)[115]	RPEMC	CSE: S: 20 µg/ml E: 4, 24 T: 4,24	XO activity ↑ 4 and 24 hrs mRNA XO ↑ 6 hrs
Li XY (1994)[116]	A549 cell line	CSE: S: 1 E: 1-6 T: 1, 4, 6 and 24 hrs after wash	EP**:↑ 1 hr, prevented by GSH, = 24 hrs after wash GSH intracellular ↓, = 24 hrs after wash

Noronha-Dutra A (1993)[117]	HUVEC	CSE: S: 0.5 E: 30 min T: 30 min	Pentose phosphate pathway activated GSSG release ↑
Pinot F (1999)[118]	Human peripheral blood monocytes	CSE: S:0.006-0.024 E: overnight T: direct after	O^{2-} production =, HSP 70 ↑ Membrane pseudopodes ↓, submembrane vacuoles ↑ Surfactant prevents effects CSE
Powell GM (1971)[119]	Rabbit AMs	CSE: S: ? E: ? T: ?	G3PD activity in AMs ↓, prevented by cysteine G6PD and LDH in AMs =
Rahman I (1996)[120]	A549 cell line	CSE: S: 1 puff/3 ml E: 4 T: 16-28	24 hrs after CSE intracellular: GSH ↑, GSSG =, γGCS activity ↑, γGCS-HS mRNA ↑
Tsuchiya MD (1992)[121]	Rat PMNs	CSE: S: 1 cig E: 20 min T: 20 min	ROS production from PMNs ↓, prevented by SOD O_2 consumption from PMNs ↑
Tuder RM (2000)[122]	Bovine artery endothelial cells, Monocytic U937, Hep G2, A549 cell line	CSE: S: 10% E: 24 T: 24	All cells: NO production ↑ All cells, except A549 cell line: VEGF ↓ protein and mRNA Apoptosis ↑ bovine artery endothelial cells
Wickenden JA (2003)[123]	A549 cell line HUVEC Jurkat cell	CSE: S: 0.05-0.1 E: 24 T: 24	Necrosis ↑, no apoptosis* GSH inhibits necrosis and apoptosis (Jurkat cell) GSH/GSSG ↓ intracellularly Inhibition caspase-3 activation (Jurkat cell)

Definition of abbreviations:
S: dose of smoke exposure (cig/ml). When possible, in order to compare cigarette smoke exposure between studies, the number of cigarettes per ml was calculated. E: time of smoke exposure (hrs) T: time between start of smoke exposure and measurement (hrs)

AMs: Alveolar Macrophages; AP-1: activator protein-1; AR: amphiregulin; BBEC: bovine bronchial epithelial cells; CS: cigarette smoke (gas phase); CSE cigarette smoke extract; ECV304: Human endothelial cell line; EGFR: epidermal growth factor receptor; ELAM-1: endothelial leukocyte adhesion molecule; EP: epithelial permeability; G3PD: glyceraldehydes 3-phosphate dehydrogenase; G6PD: glucose-6 phosphate dehydrogenase; γ-GCS-HS: γ-glutamylcysteine synthetase heavy subunit; GM-CSF: granulocyte-macrophage colony-stimulating factor; GSH: gluthatione; GSSG: oxidised gluthatione; GSTP1: gluthatione S-transferase P1; HBEC: human bronchial epithelial cell; HB-EGF: heparin-binding EGF like growth factor; trHBMECs: transfected human bone marrow endothelial cells; HFL1: human fetal lung fibroblasts; HSP 70: heat shock protein 70; HUVEC: human umbilical vein endothelial cells; ICAM-1: intercellular adhesion molecule 1; IFN-γ: interferon gamma; LA-4: murine lung epithelial cell line; LDH: lactate dehydrogenase; LTB4: leukotrien B4; NAC: N-acetylcysteine; NCI:H292: Human pulmonary

mucoepidermoid carcinoma cell-line; NE: neutrophil elastase; NO: nitric oxide; PBMCs: peripheral blood mononuclear cells; PMs: peritoneal macrophages; PMNs: polymorphonuclear cells; RANTES: regulated on activation normal T-cell expressed and presumably secreted; ROS: radical oxidant scavengers; RPMEC: rat pulmonary micro vascular endothelial cells; sICAM: soluble intercellular adhesion molecule; SOD: superoxide dismutase; TGF-α: transforming growth factor α; TNF-α: tumor necrosis factor α; TUNEL: terminal deoxynucleotidyl transferase-mediated dUTP nick end labelling; U-937: premonocyte cell line; VCAM-1: vascular cell adhesion molecule 1; VEGF: vascular endothelial growth factor; XO: xanthine oxidase.

[*] Light microscopy, TUNEL and EM
[†] Attachment and migration to fibronectin-coated dishes
[‡] Annexin V
[§] 7-AAD uptake
[ll] Attachment/detachment to plastic
[¶] Functional adherence to A549 cell line

1 Abboud RT, Fera T, Johal S, *et al*. Effect of smoking on plasma neutrophil elastase levels. *J Lab Clin Med* 1986;108:294-300.

2 Drost EM, Selby C, Bridgeman MME, *et al*. Decreased leukocyte deformability after acute cigarette smoking in humans. *Am Rev Respir Dis* 1993;148:1277-83.

3 Fauler J, Frolich JC. Cigarette smoking stimulates cysteinyl leukotriene production in man. *Eur J Clin Invest* 1997;27:43-7.

4 Gil E, Chen B, Kleerup E, *et al*. Acute and chronic effects of marijuana smoking on pulmonary alveolar permeability. *Life Sci* 1995;56:2193-9.

5 Hockertz S, Emmendorffer A, Scherer G, *et al*. Acute effects of smoking and high experimental exposure to environmental tobacco smoke (ETS) on the immune system. *Cell Biol Toxicol* 1994;10:177-90.

6 Kaplan JD, Calandrino FS, Schuster DP. Effect of smoking on pulmonary vascular permeability. A positron emission tomography study. *Am Rev Respir Dis* 1992;145:712-5.

7 Kobayashi J, Kihira Y, Kitamura S. Effects of cigarette smoking on blood levels of leukotrienes and plasma levels of complements C3a and C5a in healthy volunteers. *Arch Environ Health* 1988;43:371-4.

8 Janoff A, Raju L, Dearing R. Levels of elastase activity in bronchoalveolar lavage fluids of healthy smokers and nonsmokers. *Am Rev Respir Dis* 1983;127:540-4.

9 MacNee W, Wiggs B, Belzberg AS, *et al*. The effect of cigarette smoking on neutrophil kinetics in human lungs. *N Engl J Med* 1989;321:924-8.

10 Patiar S, Slade D, Kirkpatrick U, *et al*. Smoking causes a dose-dependent increase in granulocyte-bound L- selectin. *Thromb Res* 2002;106:1-6.

11 Skwarski KM, Gorecka D, Sliwinski P, *et al*. The effects of cigarette smoking on pulmonary hemodynamics. *Chest* 1993;103:1166-72.

12 Tardif J, Borgeat P, Laviolette M. Inhibition of human alveolar macrophage production of leukotriene B4 by acute in vitro and in vivo exposure to tobacco smoke. *Am J Respir Cell Mol Biol* 1990;2:155-61.

13 Walter S, Nancy NR. Basopenia following cigarette smoking. *Indian J Med Res* 1980;72:422-5.

14 Walter S, Walter A. Basophil degranulation induced by cigarette smoking in man. *Thorax* 1982;37:756-9.

15 Ward C. Bronchoalveolar lavage fluid urea as a marker of pulmonary permeability in healthy smokers. *Eur Respir J* 2000;15:285.

16 Winkel P, Statland BE. The acute effect of cigarette smoking on the concentrations of blood leukocyte types in healthy young women. *Am J Clin Pathol* 1981;75:781-5.

17 Balint B, Donnelly LE, Hanazawa T, *et al*. Increased nitric oxide metabolites in exhaled breath condensate after exposure to tobacco smoke. *Thorax* 2001;56:456-61.

18 Chambers DC, Tunnicliffe WS, Ayres JG. Acute inhalation of cigarette smoke increases lower respiratory tract nitric oxide concentrations. *Thorax* 1998;53:677-9.

19 Guatura SB, Martinez JA, Santos Bueno PC, *et al*. Increased exhalation of hydrogen peroxide in healthy subjects following cigarette consumption. *Sao Paulo Med J* 2000;118:93-8.

20 Kharitonov SA, Robbins RA, Yates D, *et al*. Acute and chronic effects of cigarette smoking on exhaled nitric oxide. *Am J Respir Crit Care Med* 1995;152:609-12.

21 Morrison D, Rahman I, Lannan S, *et al*. Epithelial permeability, inflammation, and oxidant stress in the air spaces of smokers. *Am J Respir Crit Care Med* 1999;159:473-9.

22 Morrow JD, Frei B, Longmire AW, *et al*. Increase in circulating products of lipid peroxidation (F2- isoprostanes) in smokers. Smoking as a cause of oxidative damage. *N Engl J Med* 1995;332:1198-203.

23 Montuschi P, Collins JV, Ciabattoni G, *et al*. Exhaled 8-isoprostane as an in vivo biomarker of lung oxidative stress in patients with COPD and healthy smokers. *Am J Respir Crit Care Med* 2000;162:1175-7.

24 Rahman I, Morrison D, Donaldson K, *et al*. Systemic oxidative stress in asthma, COPD, and smokers. *Am J Respir Crit Care Med* 1996;154:1055-60.

25 Tsuchiya M, Asada A, Kasahara E, *et al*. Smoking a single cigarette rapidly reduces combined concentrations of nitrate and nitrite and concentrations of antioxidants in plasma. *Circulation* 2002;105:1155-7.

26 Abrams WR, Kucich U, Kimbel P, *et al*. Acute cigarette smoke exposure in dogs: the inflammatory response. *Exp Lung Res* 1988;14:459-75.

27 Bosken CH, Doerschuk CM, English D, *et al*. Neutrophil kinetics during active cigarette smoking in rabbits. *J Appl Physiol* 1991;71:630-7.

28 Boucher RC, Johnson J, Inoue S, *et al*. The effect of cigarette smoke on the permeability of guinea pig airways. *Lab Invest* 1980;43:94-100.

29 Burns AR, Hosford SP, Dunn LA, *et al*. Respiratory epithelial permeability after cigarette smoke exposure in guinea pigs. *J Appl Physiol* 1989;66:2109-16.

30 Churg A, Zay K, Shay S, *et al*. Acute cigarette smoke-induced connective tissue breakdown requires both neutrophils and macrophage metalloelastase in mice. *Am J Respir Cell Mol Biol* 2002;27:368-74.

31 Churg A, Dai J, Tai H, *et al*. Tumor necrosis factor-alpha is central to acute cigarette smoke-induced inflammation and connective tissue breakdown. *Am J Respir Crit Care Med* 2002;166:849-54.

32 Churg A, Wang RD, Tai H, *et al*. Macrophage metalloelastase mediates acute cigarette smoke-induced inflammation via tumor necrosis factor-alpha release. *Am J Respir Crit Care Med* 2003;167:1083-9.

33 Daffonchio L, Hernandez A, Omini C. Sensory neuropeptides are involved in cigarette smoke induced airway hyperreactivity in guinea-pig. *Agents Actions Suppl* 1990;31:215-22.

34 Dhami R, Gilks B, Xie C, *et al*. Acute cigarette smoke-induced connective tissue breakdown is mediated by neutrophils and prevented by alpha1-antitrypsin. *Am J Respir Cell Mol Biol* 2000;22:244-52.

35 Holt PG, Keast D. Acute effects of cigarette smoke on murine macrophages. *Arch Environ Health* 1973;26:300-4.

36 Hulbert WC, Walker DC, Jackson A, *et al*. Airway permeability to horseradish peroxidase in guinea pigs: the repair phase after injury by cigarette smoke. *Am Rev Respir Dis* 1981;123:320-6.

37 Ishizaki T, Kishi Y, Sasaki F, *et al*. Effect of probucol, an oral hypocholesterolaemic agent, on acute tobacco smoke inhalation in rats. *Clin Sci (Lond)* 1996;90:517-23.

38 Janoff A, Carp H, Lee DK, *et al*. Cigarette smoke inhalation decreases alpha 1-antitrypsin activity in rat lung. *Science* 1979;206:1313-4.

39 Kew RR, Ghebrehiwet B, Janoff A. The role of complement in cigarette smoke-induced chemotactic activity of lung fluids. *Am Rev Respir Dis* 1986;133:478-81.

40 Kilburn KH, McKenzie W. Leukocyte recruitment to airways by cigarette smoke and particle phase in contrast to cytotoxicity of vapor. *Science* 1975;189:634-7.

41 Li XY, Rahman I, Donaldson K, *et al*. Mechanisms of cigarette smoke induced increased airspace permeability. *Thorax* 1996;51:465-71.

42 Mordelet-Dambrine M, Leguern-Stanislas G, Chinet TC, *et al*. Effects of tobacco smoke on respiratory epithelial clearance of DTPA and on lung histology in rats. *Eur Respir J* 1991;4:839-44.

43 Nishikawa M, Ikeda H, Fukuda T, *et al*. Acute exposure to cigarette smoke induces airway hyperresponsiveness without airway inflammation in guinea pigs. Dose-response characteristics. *Am Rev Respir Dis* 1990;142:177-83.

44 Ortega E, Hueso F, Collazos ME, *et al*. Phagocytosis of latex beads by alveolar macrophages from mice exposed to cigarette smoke. *Comp Immunol Microbiol Infect Dis* 1992;15:137-42.

45 Ortega E, Barriga C, Rodriguez AB. Decline in the phagocytic function of alveolar macrophages from mice exposed to cigarette smoke. *Comp Immunol Microbiol Infect Dis* 1994;17:77-84.

46 Pessina GP, Paulesu L, Corradeschi F, *et al*. Production of tumor necrosis factor alpha by rat alveolar macrophages collected after acute cigarette smoking. *Arch Immunol Ther Exp (Warsz)* 1993;41:343-8.

47 Pessina GP, Paulesu L, Corradeschi F, *et al*. Pulmonary catabolism of interleukin 6 evaluated by lung perfusion of normal and smoker rats. *J Pharm Pharmacol* 1996;48:1063-7.

48 Reznik-Schuller HM. Acute effects of cigarette smoke inhalation on the Syrian hamster lungs. *J Environ Pathol Toxicol* 1980;4:285-91.

49 Simani AS, Inoue S, Hogg JC. Penetration of the respiratory epithelium of guinea pigs following exposure to cigarette smoke. *Lab Invest* 1974;31:75-81.

50 Vitalis TZ, Kern I, Croome A, *et al*. The effect of latent adenovirus 5 infection on cigarette smoke-induced lung inflammation. *Eur Respir J* 1998;11:664-9.

51 Walker DC, Burns AR. The mechanism of cigarette smoke induced increased epithelial permeability in guinea pig airways. *Prog Clin Biol Res* 1988;263:25-34.

52 Witten ML, Lemen RJ, Quan SF, *et al*. Acute cigarette smoke exposure increases alveolar permeability in rabbits. *Am Rev Respir Dis* 1985;132:321-5.

53 Witten ML, Quan SF, Sobonya RE, *et al*. Acute cigarette smoke exposure alters lung eicosanoid and inflammatory cell concentrations in rabbits. *Exp Lung Res* 1988;14:727-42.

54 Wright J, Harrison N. Cardiopulmonary effects of a brief exposure to cigarette smoke in the guinea pig. *Respiration* 1990;57:70-6.

55 Wright JL, Farmer SG, Churg A. Synthetic serine elastase inhibitor reduces cigarette smoke-induced emphysema in guinea pigs. *Am J Respir Crit Care Med* 2002;166:954-60.

56 Yamaya M, Zayasu K, Sekizawa K, *et al*. Acute effect of cigarette smoke on cytoplasmic motility of alveolar macrophages in dogs. *J Appl Physiol* 1989;66:1172-8.

57 Aoshiba K, Koinuma M, Yokohori N, *et al*. Immunohistochemical evaluation of oxidative stress in murine lungs after cigarette smoke exposure. *Inhal Toxicol* 2003;15:1029-38.

58 Bilimoria MH, Ecobichon DJ. Protective antioxidant mechanisms in rat and guinea pig tissues challenged by acute exposure to cigarette smoke. *Toxicology* 1992;72:131-44.

59 Cavarra E, Lucattelli M, Gambelli F, *et al*. Human SLPI inactivation after cigarette smoke exposure in a new in vivo model of pulmonary oxidative stress. *Am J Physiol Lung Cell Mol Physiol* 2001;281:L412-L417.

60 Cotgreave IA, Johansson U, Moldeus P, *et al*. The effect of acute cigarette smoke inhalation on pulmonary and systemic cysteine and glutathione redox states in the rat. *Toxicology* 1987;45:203-12.

61 Uotila P. Effect of cigarette smoke on glucuronide conjugation in hamster isolated lungs. *Res Commun Chem Pathol Pharmacol* 1982;38:173-6.

62 Wright JL, Dai J, Zay K, *et al*. Effects of cigarette smoke on nitric oxide synthase expression in the rat lung. *Lab Invest* 1999;79:975-83.

63 Aoshiba K, Tamaoki J, Nagai A. Acute cigarette smoke exposure induces apoptosis of alveolar macrophages. *Am J Physiol Lung Cell Mol Physiol* 2001;281:L1392-L1401.

64 Brown GM, Drost E, Donaldson K, *et al*. Reduction of the proteolytic activity of neutrophils by exposure to cigarette smoke in vitro. *Exp Lung Res* 1991;17:923-37.

65 Bridges RB, Kraal JH, Huang LJ, *et al*. Effects of tobacco smoke on chemotaxis and glucose metabolism of polymorphonuclear leukocytes. *Infect Immun* 1977;15:115-23.

66 Cantral DE, Sisson JH, Veys T, *et al*. Effects of cigarette smoke extract on bovine bronchial epithelial cell attachment and migration. *Am J Physiol* 1995;268:L723-L728.

67 Carnevali S, Nakamura Y, Mio T, *et al*. Cigarette smoke extract inhibits fibroblast-mediated collagen gel contraction. *Am J Physiol* 1998;274:L591-L598.

68 Carnevali S, Petruzzelli S, Longoni B, *et al*. Cigarette smoke extract induces oxidative stress and apoptosis in human lung fibroblasts. *Am J Physiol Lung Cell Mol Physiol* 2003;284:L955-L963.

69 Drost EM, Selby C, Lannan S, *et al*. Changes in neutrophil deformability following in vitro smoke exposure: mechanism and protection. *Am J Respir Cell Mol Biol* 1992;6:287-95.

70 Dubar V, Gosset P, Aerts C, *et al*. In vitro acute effects of tobacco smoke on tumor necrosis factor alpha and interleukin-6 production by alveolar macrophages. *Exp Lung Res* 1993;19:345-59.

71 Falk HL, Tremer HM, Kotin P. Effect of cigarette smoke and its constituents on ciliated mucus-secreting epithelium. *J Natl Cancer Inst* 1959;23:999-1012.

72 Floreani AA, Wyatt TA, Stoner J, *et al*. Smoke and C5a induce airway epithelial intercellular adhesion molecule-1 and cell adhesion. *Am J Respir Cell Mol Biol* 2003;29:472-82.

73 Green GM, Carolin D. The depressant effect of cigarette smoke on the in vitro antibacterial activity of alveolar macrophages. *N Engl J Med* 1967;276:421-7.

74 Higashimoto Y, Shimada Y, Fukuchi Y, *et al*. Inhibition of mouse alveolar macrophage production of tumor necrosis factor alpha by acute in vivo and in vitro exposure to tobacco smoke. *Respiration* 1992;59:77-80.

75 Hellermann GR, Nagy SB, Kong X, *et al*. Mechanism of cigarette smoke condensate-induced acute inflammatory response in human bronchial epithelial cells. *Respir Res* 2002;3:22.

76 Holt PG, Keast D. The effect of tobacco smoke on protein synthesis in macrophages. *Proc Soc Exp Biol Med* 1973;142:1243-7.

77 Hoshino Y, Mio T, Nagai S, *et al*. Cytotoxic effects of cigarette smoke extract on an alveolar type II cell-derived cell line. *Am J Physiol Lung Cell Mol Physiol* 2001;281:L509-L516.

78 Ishii T, Matsuse T, Igarashi H, *et al*. Tobacco smoke reduces viability in human lung fibroblasts: protective effect of glutathione S-transferase P1. *Am J Physiol Lung Cell Mol Physiol* 2001;280:L1189-L1195.

79 Kalra VK, Ying Y, Deemer K, *et al*. Mechanism of cigarette smoke condensate induced adhesion of human monocytes to cultured endothelial cells. *J Cell Physiol* 1994;160:154-62.

80 Kim HJ, Liu X, Wang H, *et al*. Glutathione prevents inhibition of fibroblast-mediated collagen gel contraction by cigarette smoke. *Am J Physiol Lung Cell Mol Physiol* 2002;283:L409-L417.

81 Koyama S, Rennard SI, Leikauf GD, *et al*. Bronchial epithelial cells release monocyte chemotactic activity in response to smoke and endotoxin. *J Immunol* 1991;147:972-9.

82 Lannan S, McLean A, Drost E, *et al*. Changes in neutrophil morphology and morphometry following exposure to cigarette smoke. *Int J Exp Pathol* 1992;73:183-91.

83 Lannan S, Donaldson K, Brown D, *et al*. Effect of cigarette smoke and its condensates on alveolar epithelial cell injury in vitro. *Am J Physiol* 1994;266:L92-100.

84 Marwick JA, Kirkham P, Gilmour PS, *et al*. Cigarette smoke-induced oxidative stress and TGF-beta1 increase p21waf1/cip1 expression in alveolar epithelial cells. *Ann N Y Acad Sci* 2002;973:278-83.

85 Masubuchi T, Koyama S, Sato E, *et al*. Smoke extract stimulates lung epithelial cells to release neutrophil and monocyte chemotactic activity. *Am J Pathol* 1998;153:1903-12.

86 Mio T, Romberger DJ, Thompson AB, *et al*. Cigarette smoke induces interleukin-8 release from human bronchial epithelial cells. *Am J Respir Crit Care Med* 1997;155:1770-6.

87 Nakamura Y, Romberger DJ, Tate L, *et al*. Cigarette smoke inhibits lung fibroblast proliferation and chemotaxis. *Am J Respir Crit Care Med* 1995;151:1497-503.

88 Niki E, Minamisawa S, Oikawa M, *et al*. Membrane damage from lipid oxidation induced by free radicals and cigarette smoke. *Ann N Y Acad Sci* 1993;686:29-37.

89 Zhang X, Wang L, Zhang H, *et al*. The effects of cigarette smoke extract on the endothelial production of soluble intercellular adhesion molecule-1 are mediated through macrophages, possibly by inducing TNF-alpha release. *Methods Find Exp Clin Pharmacol* 2002;24:261-5.

90 Richter A, O'Donnell RA, Powell RM, *et al*. Autocrine ligands for the epidermal growth factor receptor mediate interleukin-8 release from bronchial epithelial cells in response to cigarette smoke. *Am J Respir Cell Mol Biol* 2002;27:85-90.

91 Robbins RA, Koyama S, Spurzem JR, *et al*. Modulation of neutrophil and mononuclear cell adherence to bronchial epithelial cells. *Am J Respir Cell Mol Biol* 1992;7:19-29.

92 Rusznak C, Mills PR, Devalia JL, *et al*. Effect of cigarette smoke on the permeability and IL-1beta and sICAM-1 release from cultured human bronchial epithelial cells of never- smokers, smokers, and patients with chronic obstructive pulmonary disease. *Am J Respir Cell Mol Biol* 2000;23:530-6.

93 Rusznak C, Sapsford RJ, Devalia JL, *et al*. Interaction of cigarette smoke and house dust mite allergens on inflammatory mediator release from primary cultures of human bronchial epithelial cells. *Clin Exp Allergy* 2001;31:226-38.

94 Ryder MI, Fujitaki R, Lebus S, *et al*. Alterations of neutrophil L-selection and CD18 expression by tobacco smoke: implications for periodontal diseases. *J Periodontal Res* 1998;33:359-68.

95 Ryder MI, Saghizadeh M, Ding Y, *et al*. Effects of tobacco smoke on the secretion of interleukin-1beta, tumor necrosis factor-alpha, and transforming growth factor-beta from peripheral blood mononuclear cells. *Oral Microbiol Immunol* 2002;17:331-6.

96 Sato E, Koyama S, Takamizawa A, *et al*. Smoke extract stimulates lung fibroblasts to release neutrophil and monocyte chemotactic activities. *Am J Physiol* 1999;277:L1149-L1157.

97 Selby C, Drost E, Brown D, *et al*. Inhibition of neutrophil adherence and movement by acute cigarette smoke exposure. *Exp Lung Res* 1992;18:813-27.

98 Shen Y, Rattan V, Sultana C, *et al*. Cigarette smoke condensate-induced adhesion molecule expression and transendothelial migration of monocytes. *Am J Physiol* 1996;270:H1624-H1633.

99 Shoji S, Ertl RF, Koyama S, *et al*. Cigarette smoke stimulates release of neutrophil chemotactic activity from cultured bovine bronchial epithelial cells. *Clin Sci (Lond)* 1995;88:337-44.

100 Takeyama K, Jung B, Shim JJ, *et al*. Activation of epidermal growth factor receptors is responsible for mucin synthesis induced by cigarette smoke. *Am J Physiol Lung Cell Mol Physiol* 2001;280:L165-L172.

101 Thomas WR, Holt PG, Keast D. Cigarette smoke and phagocyte function: effect of chronic exposure in vivo and acute exposure in vitro. *Infect Immun* 1978;20:468-75.

102 Vayssier M, Banzet N, Francois D, *et al*. Tobacco smoke induces both apoptosis and necrosis in mammalian cells: differential effects of HSP70. *Am J Physiol* 1998;275:L771-L779.

103 Vayssier-Taussat M, Camilli T, Aron Y, *et al*. Effects of tobacco smoke and benzo[a]pyrene on human endothelial cell and monocyte stress responses. *Am J Physiol Heart Circ Physiol* 2001;280:H1293-H1300.

104 Voisin C, Aerts C, Fournier E, *et al*. Acute effects of tobacco smoke on alveolar macrophages cultured in gas phase. *Eur J Respir Dis Suppl* 1985;139:76-81.

105 Wang HY, Ye YN, Zhu M, *et al*. Increased interleukin-8 expression by cigarettesmoke extract in endothelial cells. *Environmental Toxicology and Pharmacology* 2000;9:19-23.

106 Witherden IR, Goldstraw P, Pastorino U, *et al*. Interleukin-8 release by primary human alveolar type II cells in vitro: effect of neutrophil elastase and cigarette smoke[abstract]. *Respir Med* 1997;91:A27.

107 Wirtz HR, Schmidt M. Acute influence of cigarette smoke on secretion of pulmonary surfactant in rat alveolar type II cells in culture. *Eur Respir J* 1996;9:24-32.

108 Yeager H, Jr. Alveolar cells: depression effect of cigarette smoke on protein synthesis. *Proc Soc Exp Biol Med* 1969;131:247-50.

109 York GK, Arth C, Stumbo JA, *et al*. Pulmonary macrophage respiration as affected by cigarette smoke and tobacco extract. *Arch Environ Health* 1973;27:96-8.

110 Zappacosta B, Persichilli S, Minucci A, *et al*. Effect of aqueous cigarette smoke extract on the chemiluminescence kinetics of polymorphonuclear leukocytes and on their glycolytic and phagocytic activity. *Luminescence* 2001;16:315-9.

111 Ouyang Y, Virasch N, Hao P, *et al*. Suppression of human IL-1beta, IL-2, IFN-gamma, and TNF-alpha production by cigarette smoke extracts. *J Allergy Clin Immunol* 2000;106:280-7.

112 Bridgeman MME, Marsden M, Drost E, *et al*. The effect of cigarette smoke on lung cells[abstract]. *Am Rev Respir Dis* 1991;143:A737.

113 Hobson J, Wright J, Churg A. Histochemical evidence for generation of active oxygen species on the apical surface of cigarette-smoke-exposed tracheal explants. *Am J Pathol* 1991;139:573-80.

114 Hoyt JC, Robbins RA, Habib M, *et al*. Cigarette smoke decreases inducible nitric oxide synthase in lung epithelial cells. *Exp Lung Res* 2003;29:17-28.

115 Kayyali US, Budhiraja R, Pennella CM, *et al*. Upregulation of xanthine oxidase by tobacco smoke condensate in pulmonary endothelial cells. *Toxicol Appl Pharmacol* 2003;188:59-68.

116 Li XY, Donaldson K, Rahman I, *et al*. An investigation of the role of glutathione in increased epithelial permeability induced by cigarette smoke in vivo and in vitro. *Am J Respir Crit Care Med* 1994;149:1518-25.

117 Noronha-Dutra AA, Epperlein MM, Woolf N. Effect of cigarette smoking on cultured human endothelial cells. *Cardiovasc Res* 1993;27:774-8.

118 Pinot F, Bachelet M, Francois D, *et al*. Modified natural porcine surfactant modulates tobacco smoke-induced stress response in human monocytes. *Life Sci* 1999;64:125-34.

119 Powell GM, Green GM. Investigation on the effects of cigarette smoke on rabbit alveolar macrophages. *Biochem J* 1971;124:26P-7P.

120 Rahman I, Smith CA, Lawson MF, *et al*. Induction of gamma-glutamylcysteine synthetase by cigarette smoke is associated with AP-1 in human alveolar epithelial cells. *FEBS Lett* 1996;396:21-5.

121 Tsuchiya M, Thompson DF, Suzuki YJ, *et al*. Superoxide formed from cigarette smoke impairs polymorphonuclear leukocyte active oxygen generation activity. *Arch Biochem Biophys* 1992;299:30-7.

122 Tuder RM, Wood K, Taraseviciene L, *et al*. Cigarette smoke extract decreases the expression of vascular endothelial growth factor by cultured cells and triggers apoptosis of pulmonary endothelial cells. *Chest* 2000;117:241S-2S.

123 Wickenden JA, Clarke MC, Rossi AG, *et al*. Cigarette smoke prevents apoptosis through inhibition of caspase activation and induces necrosis. *Am J Respir Cell Mol Biol* 2003.